A systematic review on the application of cardiovascular risk prediction models in pharmacoeconomics, with a focus on primary prevention

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OBJECTIVES: Crohn's disease is a chronic relapsing-remitting inflammatory bowel disease with heterogeneous disease course, requiring life-long treatment. Phenotypes explaining disease heterogeneity is of interest in optimizing allocation of health care resources, e.g. to avoid expensive maintenance treatment to prolong remission in patients who seldom relapse. To develop economic models for evaluation of treatments, our objective was to estimate parameters of a Markov chain from data on disease activity and resource consumption and to improve model fit by allowing different phenotypes. **METHODS:** We had individual data on relapse and remission, surgery, use of medicines and other resources, aggregated over three month periods, from inflammatory bowel disease patients from 1991 and ten year onwards. Data from Crohn's disease patients were extracted. An exact maximum likelihood estimator using observations aggregated over time was used to estimate monthly transition probabilities. This estimator was adjusted to allow different disease phenotypes using an Expectation-Maximization method which identifies the phenotypes that best describe patient heterogeneity. The estimated parameters were used to derive the mean durations of a relapse and a period of remission to describe the phenotypes. **RESULTS:** At least two distinct phenotypes were found in each country, seldom-relapsing (<once/3 years) and often-relapsing (>once/3 years). The best fit was with four phenotypes in Denmark, three phenotypes in the Netherlands and in Italy, and two in Norway, Israel, Ireland, Spain, and Greece. In Denmark and Italy there was a single seldom-relapsing phenotype and more than one often-relapsing phenotype. In Netherlands there was two seldom-relapsing phenotypes. Denmark, The Netherlands, Israel, Ireland and Italy have roughly as many seldom-relapsing as often-relapsing patients. Norway, Spain and Greece have a majority of seldom-relapsing patients. **CONCLUSIONS:** Allowing for different phenotypes improves model fit. Health care resource allocation can be optimized using phenotypes. Using data aggregated over time appears to remain a challenge.

PRM39

EVALUATION OF PATIENT CENTERED OUTCOMES USING INDIVIDUAL DATA FROM A QUALITY REGISTRY AND PATIENT REPORTED ABILITIES AND RATINGS OF QUALITY IN HEALTH CARE, IN DIABETES PATIENTS IN SWEDEN

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OBJECTIVES: The Swedish National Diabetes Register (NDR) has since 1996 longitudinally recorded medical outcomes e.g. risk factors, comorbidities, and covers the majority (80%) of Swedish diabetes patients. In addition patient reported values were collected alongside the registry in a questionnaire. Our purpose was to evaluate a method for measuring patient reported abilities and ratings of quality in health care and evaluating them together with outcomes extracted from the NDR. **METHODS:** A questionnaire was developed to measure if diabetes care is percieved as patient focused and efficient, through questions on self management ability, worries, ability to carry out daily acitivites, and perception of service, access and involvement. The questionnaire was issued to 4,760 patients, 2,916 responded. Registry data on risk factors (HbA1c, blood pressure, cholesterol) were extracted for each patient and connected to the questionnaire. Item Response Theory (IRT) was used to estimate patient abilities and patient ratings of quality in health care (IRT scores) from the response patterns. For each patient, registry data and IRT scores were used to derive an overall Malmquist approach output quantity index, a health care related component and a patient ability component. The index is a measurement of how efficiently the patient leads his or her life with diabetes and its care, and provides a measure of the patient's state of health in relation to the patient's situation. **RESULTS:** We obtained IRT scale models with good fit, satisfactory validated in another population. The IRT scores provide basis for patient evaluation in a broader perspective than risk factors alone. The ability index component varies more than the health care component. **CONCLUSIONS:** The questionnaire provides estimates of abilities and ratings of quality. Our approach allows estimating patient benefit and health care production using combined registry and patient reported data, the procedure probably easier for patients than methods like time trade-off.

PRM40

EFFICACY OF LIRAGLUTIDE COMPARED TO EXENATIDE AND INSULIN GLARGINE IN PATIENTS WITH DIABETES TYPE 2: A META-ANALYSIS

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OBJECTIVES: liraglutide and exenatide are the two known approved GLP-1 analogue drug in the management of diabetes, a network meta-analysis was performed to get a more robust evidence on the efficacy of liraglutide compared to exenatide in achieving HbA1c < 7.0% in more diabetic patient. **METHODS:** Electronic database was browsed for available material on the proposed subject until May 2012, the inclusion criteria were phase 3 randomise controlled trials in diabetes type 2 patients. The software ADDIS 1.14 (Aggregate Data Drug Information System) was used to perform the network meta-analysis of liraglutide, exenatide and insulin glargin. **RESULTS:** Node-splitting analyses showed that were no relevant inconsistency in the evidence. A consistency model was used to draw conclusion about the relative effect of the three treatments. The relative risk (RR) of liraglutide compared to exenatide is 1.28 (0.57, 2.82), RR of liraglutide compared to insulin glargine is 1.72 (0.70, 4.37) and the RR of exenatide compared to insulin glargine is 1.35 (0.66, 2.76). A vague prior for the study specific baseline (α) and the treatment effect coefficients (β) are $\alpha \sim$ N (0, 3.563E-3) and $\beta \sim$ N (0, 3.563E-3) respectively. The rank probability of the three drugs ranked liraglutide first, exenatide second and insulin glargine as the last in rank of the best treatments. **CONCLUSIONS:** Liraglutide is still effective in maintaining the HbA1c < 7.0% in more diabetes patients compared to exenatide and insulin glargine however exenatide once weekly seems to be more convenient to administer and has a cost advantage compared to liraglutide once daily dose. Liraglutide dose may need to be modified to once weekly or once monthly dose to me more effective in the management of diabetes type 2.

PRM41

DESIGNING PATIENT REGISTRIES: A CASE-STUDY USING AN ONLINE INTERACTIVE DATA ANALYSIS TOOL

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OBJECTIVES: Planning and designing patient registries requires significant research to determine the type and amount of data to collect, identifying recruitment sites, understanding the impact of study criteria on sample size, and estimating patient retention. Our objective was to test the utility of a new tool for answering these questions in a timely and cost-efficient manner, and to examine how claims data can be leveraged to plan registry design. **METHODS:** We used an online interactive data analysis tool, *MarketScan®Treatment Pathways*, to explore the characteristics and health care utilization patterns in a sample of cancer patients with pain. Patients newly diagnosed with prevalent cancers that are highly associated with pain such as multiple myeloma, colorectal, lung, prostate, or breast cancer were included, if they had at least 2 ICD-9 codes for one of the cancers on different days within 60 days of each other. A 6-month pre-period without any cancer diagnosis was used to identify new cancer patients. **RESULTS:** Of the 365,980 cancer patients meeting the entry criteria, 54% had an ICD-9 code for pain-related diagnosis. The median and mean number of days from cancer to pain diagnosis was 113 and 192 days, respectively. Only 3% had a co-morbidity that would exclude participation in the registry. Nearly 64% patients had an outpatient office visit within 30-days, of them, 68% had a subsequent visit in the following 30-days. Patient diagnoses, medications and procedures were described for the 60-day period following cancer pain diagnosis. The full analysis took 6 hours including all iterations on study criteria, and outputting descriptive data on patient demographic and clinical characteristics. **CONCLUSIONS:** Using *MarketScan®Treatment Pathways*, we tested sample selection criteria and health care utilization in a fraction of time than typical database analyses. These data answered critical questions in the study design for a planned cancer pain registry in a timely and cost-efficient way.

PRM42

MANAGING A SYSTEMATIC LITERATURE REVIEW PROJECT

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OBJECTIVES: A systematic literature review (SLR) is a well-established tool for identifying and assimilating existing evidence or identifying gaps that need to be filled by new research. Although SLRs are widely used in the drug reimbursement sphere, there are many challenges in maximizing its value and in communicating project objectives with a vendor. The objective of this study is to outline the deliverables of a SLR, and examine the optimal methodology in extracting maximum value from a SLR review by exploring important caveats and pitfalls of two hypothetical case studies. **METHODS:** Two hypothetical case studies are used to outline the process and the pitfalls of a SLR project and the relationship between industry and vendor. Feedback was elicited from consultants and industry in order to identify expectations and advice for a successful systematic literature review. **RESULTS:** The analysis found that in depth discussion during the protocol phase of the SLR is crucial to the success of the project. A successful protocol will incorporate: key questions that are focused and specific, scoping to outline the search strategy, and address the purpose of the review in terms of a product's value story (ie. a SLR for inclusion in a GVD), or evidence development. The analysis found that some challenges include too much or too little literature, which can be due to a very broad or narrow research question, challenges that arise due to expectations for certain data, and addressing gaps in the literature. Several suggestions on overcoming these challenges and caveats of the methodology are explored through the hypothetical case studies. **CONCLUSIONS:** The authors found that communication and a focused question were the most helpful in yielding successful literature reviews. Furthermore, detailed discussion at the protocol stage helped to avoid pitfalls at later points in SLR development. The authors provide a list of pitfalls and remedies that may help when considering SLRs.

RESEARCH ON METHODS - Modeling Methods

PRM43

A SYSTEMATIC REVIEW ON THE APPLICATION OF CARDIOVASCULAR RISK PREDICTION MODELS IN PHARMACOECONOMICS, WITH A FOCUS ON PRIMARY PREVENTION

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OBJECTIVES: In the absence of long-term randomized clinical trials (RCTs) on the effectiveness of pharmacological treatment for primary cardiovascular disease (CVD) prevention, risk prediction models are used to project changes in CVD incidence due to changes on risk factor levels observed in short-term RCTs. This study aims to summarize the literature on the application of these CVD risk models in pharmacoeconomic studies for primary CVD prevention interventions in high in-

come countries. **METHODS:** We systematically reviewed the literature on the application of CVD risk models in pharmacoeconomic studies. We assessed the quality of incorporation of risk models in these studies by evaluating the agreement of the population characteristics and the time horizon applied between the risk model and the pharmacoeconomic study, the appropriateness of the risk model for the population studied, and the incorporation of the uncertainty of the risk model in the sensitivity analysis. **RESULTS:** We identified 12 studies using published CVD risk models. The studies demonstrated the usefulness of projecting intermediate effectiveness endpoints to long term, health and cost related, benefits. However, our quality assessment highlighted the distance between the populations of the risk model and the studies reviewed, the disagreement between risk model and study time horizons, and the lack of consideration of all uncertainty surrounding risk predictions. **CONCLUSIONS:** Given that utilizing a risk model to project the effect of a pharmacological intervention to CVD events provides an estimate of the intervention's clinical and economic impact, consideration should be paid on the agreement between the study and risk model populations as well as the level of uncertainty that these predictions add to the decision-analytic model. In the absence of hard endpoint trials, the value of risk models to model pharmacological efficacy in primary CVD prevention remains high, although their limitation should be acknowledged.

PRM44

INCREASING LIFE EXPECTANCY: IMPLICATIONS FOR COST-EFFECTIVENESS ANALYSIS

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OBJECTIVES: In developed countries mortality in the general population has been declining for several decades and is anticipated to decrease further, especially among the elderly. Life tables based on national statistics reflect mortality conditions of a particular year and therefore do not take into account that survival increases in the general population. As a consequence, life tables seem to systematically underestimate overall survival of the general population. Health economic models use life tables to predict survival of the general population and may therefore also underestimate survival. Our study compares survival prediction methods and discuss implications for health economic models. **METHODS:** Period life expectancy at age 50 calculated from Dutch mortality rates published for 2009 was compared with life expectancy of a cohort aged 50 in 2009 calculated from projected mortality rates forecasted by the standard Lee-Carter approach. The Lee-Carter model forecasts the level and age pattern of mortality based on the combination of singular value decomposition of mortality rates and statistical time series methods. Mortality rates were taken from the Human Mortality Database. Projections were based on historical data between 1970 and 2009. **RESULTS:** Based on projected mortality, cohort life expectancy was 34.97 years whereas period life expectancy was only 32.37 years (−2.60 years). When life years were discounted at a 1.5% rate, the corresponding values were 25.31 and 26.40 years (−1.09 years). **CONCLUSIONS:** The analyses shows that taking into account the decrease in survival over time results in a difference of 7% in undiscounted and 4% in discounted life expectancy in the Netherlands. This difference can have a substantial impact on cost-effectiveness results, especially of curative interventions for diseases that are life threatening or of prevention programmes over a long time horizon. In these cases, sensitivity analysis should be carried out to investigate the impact of decreasing mortality.

PRM45

UTILITY ESTIMATION FOR VISUAL ACUITY HEALTH STATES: AN ORIGINAL AND PRAGMATIC APPROACH TO TRANSPOSE PUBLISHED EVIDENCE INTO A MORE FLEXIBLE ESTIMATION

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OBJECTIVES: The NICE reference case stipulates cost-utility analysis as the preferred form of economic evaluation, with health effects expressed in QALYs and health states valued using a validated choice-based method such as the time-trade-off (TTO). The evidence-base describing the impact of visual impairment (VI) on quality-of-life is very limited. To date, the Czoski-Murray et al. (2009) utility values for 4 visual health severity groups are considered the most plausible set of utility values for use in eye-disorder economic models. These utility values, originally elicited through simulating VI similar to that associated with wet age-related macular degeneration, were recently applied in other retinal disorders such as diabetic macular edema. The objective of our analysis was to refine the mapping of utilities onto visual acuity (VA). **METHODS:** OLS regression models were built to estimate the relationship between mid-point VA of 4 visual health severity groups and mean TTO scores as described in the literature. Linear and non-linear approaches for utility estimation as a function of the number of VA letters were explored. **RESULTS:** The linear regression for utility estimation was found to be statistically significant. The beta-coefficient for mid-point VA was 0.0054 ($p=0.030$) and 0.2864 for the constant term ($p=0.034$). Linear regression estimates were used to predict the utility value for 6 pre-specified VA health states: VA1 (0.766); VA2 (0.671); VA3 (0.616); VA4 (0.562); VA5 (0.507); VA6 (0.382). **CONCLUSIONS:** Published evidence on utility values for deterministic visual health severity groups may not easily transpose to alternative vision health-states. Our analysis demonstrated an original approach for utility estimation allowing a more flexible and robust method to map previously elicited VA-associated utilities onto alternate VA health-states. This method allows wider applicability of VA-associated utility estimation in other eye disorders characterized by VA impairment such as vitreomacular traction and macular hole.

PRM46

DEVELOPMENT OF A FRAMEWORK FOR COST-EFFECTIVENESS ANALYSIS COHORT SIMULATION USING AN ORDINARY DIFFERENTIAL EQUATION SOLVER ALGORITHM IN R

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OBJECTIVES: Dynamical processes in cost-effectiveness analysis (CEA) are typically described using Markov models that account for the full stochastic nature of the process, or alternatively using systems of ordinary differential equations (ODEs). In CEAs, ODEs are useful for defining dynamical systems with complex, time-varying properties that often need to be considered, and are difficult to implement as Markov models. However, in the field of CEA, fixed step sizes ('cycle lengths') are used for solving systems of ODEs, which may result in bias if the step size is too large in relation to the magnitude of change. The aim of this project was to implement and demonstrate the use of a well established dynamical ODE solver algorithm (LSODA) for CEAs in the statistical scripting language R, and to quantify bias in outcome caused by use of a fixed-step size cohort simulation approach. **METHODS:** To demonstrate the proposed approach, a previously reported CEA on adjuvant breast cancer therapies was re-analysed using the ODE solver algorithm LSODA. A model implementing the fixed-cycle length method was also developed to compare bias by using a range of different cycle lengths. **RESULTS:** The CEA model was successfully developed using the ODE solver LSODA. The use of fixed cycle lengths resulted in bias compared to the outcome of the ODE model. A cycle length of 1 year resulted in an underestimation of 0.016 absolute LYs (5.6%) and €158 (6.8%) compared to the dynamical-step size model. **CONCLUSIONS:** The developed dynamical approach was found to be suitable for conduct of CEA's and flexible in use. Moreover, it was demonstrated that use of fixed cycle lengths could potentially cause unnecessary bias in CEA outcomes. Finally, we advocate use of scripting languages such as R in the field of health economics to improve transparency, reproducibility and overall integrity of conducted CEAs.

PRM47

COST-EFFECTIVENESS UNCERTAINTY ANALYSIS METHODS: A COMPARISON OF ONE-WAY SENSITIVITY, ANALYSIS OF COVARIANCE, AND EXPECTED VALUE OF PARTIAL PERFECT INFORMATION

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OBJECTIVES: To compare cost-effectiveness model input influence on incremental net monetary benefit (INMB) across three methods of uncertainty analysis: 1) one-way sensitivity analysis; 2) probabilistic analysis of covariance (ANCOVA); and 3) expected value of partial perfect information (EVPPI). **METHODS:** We replicated and expanded a published HIV/AIDS cost-effectiveness Markov model (monotherapy vs. combination therapy) using TreeAge®. Case 1 assumed a willingness-to-pay of £20,000/QALY (relatively low decision uncertainty in this application). Case 2 assumed a willingness-to-pay of £8,000/QALY (relatively high decision uncertainty). For Cases 1 and 2, one-way sensitivity analysis identified the ten most influential inputs. From these ten inputs, we estimated ANCOVA results (10,000 Monte Carlo draws) and EVPPI for each input (1,000 inner and 1,000 outer draws). For each case and method, we ranked inputs based on their influence on variation of INMB and compared input ranks within case using Spearman's rank correlation. **RESULTS:** Mean INMB was £9,740 (Case 1) and £179 (Case 2) in favor of combination therapy. Case 1: The two most influential inputs were the same across all uncertainty methods, contributed 78% of variation in outcome (ANCOVA), and were the only inputs with non-zero EVPPI values. Case 2: All inputs had non-zero EVPPI values, with the two most influential inputs accounting for 49% of variation in outcome (ANCOVA). For Cases 1 and 2, the influential input rank order correlations across uncertainty methods ranged from 0.70 to 0.99 (all p-values < 0.05 for pairwise uncertainty method correlations for both cases). **CONCLUSIONS:** For both cases, the influential input ranks were positively correlated between one-way and more advanced uncertainty analyses, indicating influential input rank agreement. Although each method provides unique information, the additional resources needed to generate and communicate advanced analyses should be weighed, especially when the outcome decision uncertainty and therefore value of information is low. (i.e. Case 1).

PRM48

THE HALF-CYCLE "CORRECTION": HOW MUCH OF A CORRECTION IS IT?

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OBJECTIVES: In economic models that use Markov-type processes, it is generally recommended that a 'half-cycle correction' be built into the analysis, to account for the fact that events can occur at any point during the cycle. This study explores the implications of the half-cycle correction, and highlights a number of flaws in the approach. **METHODS:** A brief review of health technology assessment models was undertaken to determine the use of half-cycle corrections. The study aimed to explore the theoretical, practical and mathematical implications of the half-cycle